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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/622,646	OZAKI ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _13 August 2010_.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _1-4 and 6-18_ is/are pending in the application.

4a) Of the above claim(s) _3,4,10-12 and 14-16_ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _1,2,6-9,13,17 and 18_ is/are rejected.

7)☒ Claim(s) _18_ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _21 August 2000 and 19 September 2008_ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _8/13/10_.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/13/2010 has been entered.

2. Claim 1 was amended. New claim 18 has been added. Accordingly, claims 1-4 and 6-18 are pending in the application with claims 3-4, 10-12, and 14-16 currently withdrawn. Claims 1-2, 6-9, 13, and 17-18 are subject to examination below in light of the elected species of *a protein having the amino acid sequence modified by lacking __17__ amino acid residues from the C-terminal of SEQ ID NO:20.*

Priority

3. The present application was filed on 8/21/00 and is a national stage (371) entry of PCT/JP99/00885, filed 2/25/99. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 10-60613, filed on 2/25/98 in Japan.

Claim Objections

4. Claim 18 is objected to because of the following informalities:

Claim 18 recites that "the fluids is selected from…", which lacks proper subject-verb agreement.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-2, 6-7, 13, and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 7, 555, 560-577, and 591-592) in view of Ishikawa et al. ("Molecular cloning and chromosomal mapping of a bone marrow stromal cell surface gene, BST2, that may be involved in pre-B-cell growth" Genomics. 1995 Apr 10;26(3):527-34), Gastinel et al. (U.S. 5,623,053), Lauffer et al. (U.S. 5,639,597), Laping et al. (U.S. 5,866,693), Lo et al. (U.S. 5,541,087), Matsuzawa et al. (U.S. 5,374,533), and Browning et al. (WO 96/22788).

Harlow & Lane teach antibody-capture assays, in which an antigen is bound to a solid phase in order to capture specific antibody present within a test sample (see page 555, Figure 14.1 in particular; and pages 560 and 562-577). Such assays are useful, for example, in quantitating antibodies and can be used to compare the epitopes recognized by different antibodies (see especially at page 563, first paragraph).

Harlow & Lane therefore teach immunochemical assays of the same format as claimed instantly, in which an antigen is bound to a solid support and used to detect antibodies specific to the antigen in a test sample. However, Harlow & Lane fail to teach soluble HM1.24 antigen protein as the type of antigen, and similarly fail to teach anti-HM1.24 antibodies as the type of antibodies detected.

Ishikawa et al. teach the antigen BST-2, which is a human membrane protein expressed on bone marrow stromal cells (the abstract). It is noted that BST-2 as taught by Ishikawa et al. is the same protein referred to in the instant specification as HM1.24 antigen. This is evident by referring to the predicted amino acid sequence for the 180-residue BST-2 protein in Figure 4 of Ishikawa et al., which is the same sequence disclosed instantly as SEQ ID NO:16 (the full-length human HM1.24 antigen). The authors conducted functional studies which suggested that this antigen may be involved in stimulating pre-B-cell growth (abstract; page 528, left column, first paragraph; page 531, right column, first sentence; and page 532, right column, last paragraph).

When taken together with the teachings of Harlow & Lane, therefore, it would have been obvious to one of ordinary skill in the art to pursue immunochemical antibody-capture assays using the novel BST-2/HM1.24 antigen taught by Ishikawa et al. as the type of antigen in order to detect antibodies specific to BST-2/HM1.24 in a test sample according to the methods of

Harlow & Lane. One would be motivated to do this in order to quantify such antibodies and/or to compare their epitopes as part of experiments to further study a newly discovered protein of importance in pre-B-cell growth.

However, Ishikawa et al. further teach that the BST-2/HM1.24 protein is a transmembrane protein (the abstract).

Those of skill in the art at the time of the invention recognized certain technical considerations for dealing with antigens that are transmembrane proteins.

For example, Gastinel et al., in discussing the transmembrane FcRn receptor, teach that the hydrophobic nature of the receptor's transmembrane domain precludes the solubilization of the protein in aqueous buffer without the use of surfactants, which are often toxic, difficult to remove, and can reduce the stability of proteins (column 4, lines 43-50). As a result, the usefulness of the membrane-bound receptor is limited by the fact that, like other transmembrane proteins, is not readily soluble in aqueous solutions without surfactants (column 4, line 66 to column 5, line 2). By contrast, Gastinel et al. teach that there are many applications for an Fc receptor that is soluble in aqueous solutions without the use of a surfactant (column 4, lines 51-65; column 11, lines 62-67). Gastinel et al. further teach that such soluble receptors can be produced by removal of the transmembrane domain (column 5, lines 3-20; column 6, lines 1-10; column 10, lines 48-57). In addition, the soluble receptors of Gastinel et al. maintained the ability to bind to antibodies and can be attached to any compatible, functional surface (column 10, lines 42-47; column 11, lines 62-67).

Lauffer et al. discuss how binding experiments involving transmembrane receptor proteins can be carried out while the receptors remain bound to the cell, but that such assays are

increasingly difficult as the number of receptors in the cell membrane decreases (column 1, lines 8-35). To avoid this drawback, Lauffer et al. propose receptor binding assays using soluble fusion proteins in place of membrane-bound receptors, in which the extracellular domains of human membrane proteins are fused to the constant part (Fc) of the heavy chain of an Ig (column 1, line 35 to column 2, line 40). Such fusion proteins retain their biological activity (column 1, lines 62-67). The fusion proteins can be produced as secreted proteins in animal cells and easily purified by affinity chromatography via their Fc part, e.g. on a sepharose matrix (column 2, lines 4-18).

Similarly, Laping et al. teach Fc fusion proteins in which proteins or parts thereof are fused to the immunoglobulin constant or Fc region (column 9, line 55 to column 10, line 27). Laping et al. also contemplate fusion proteins involving membrane-bound receptors, in which one or more of the extracellular domain, the transmembrane domain, or the cytoplasmic domains of the receptors are used as components of the fusion protein (column 10, line 28-36).

Laping et al. further teach that for some uses, it is desirable to be able to delete the Fc part after the fusion protein has been expressed and purified (ibid; as well as the abstract and claims 9-12). This is the case when the Fc portion proves to be a hindrance, for example, when the fusion protein is to be used as an antigen. This is done by linking the two components of the fusion protein with a cleavable linking region, e.g. a cleavage sequence that can be cleaved with factor Xa.

Lo et al. also teach fusion protein expression systems that enhance the production of a given target protein, in which an encoded target protein is fused to a secretion cassette such as an

Fc domain, which allows for purification by binding to protein A. See column 1, lines 5-20; column 2, line 62 to column 2, line 56; and column 4, lines 46-60.

Lo et al. also contemplate production of essentially any target protein using this system, including target proteins that are normally non-secreted proteins. For example, if a desired target protein includes sequences encoding a secretion signal or a transmembrane signal, these sequences can be removed so that the fusion protein is secreted as a soluble protein (column 8, lines 1-21; column 1, lines 16-20). Thus, by using this Fc fusion system, a higher level of protein expression may be obtained (see also column 13, lines 50-55).

Lo et al. further teach that a proteolytic cleavage site is interposed between the encoded target protein and the Fc region, allowing it to be subsequently cleaved (ibid and column 5, lines 8-24; column 3, line 66 to column 4, line 2).

Matsuzawa et al. recognized that nonspecific interactions can occur between Fc sequences and components in a sample such as rheumatoid factor, which results in nonspecific interactions in immunoassays. See column 2, lines 9-32. To avoid this problem of nonspecific interactions, the authors removed the Fc sequence from their immunoassay reagent (in this case, an antibody). See also column 4, lines 41-55.

Finally, Browning et al. also teach methods of preparing soluble forms of a transmembrane receptor protein, in which the amino acid sequences that localize the protein have been deleted or inactivated; such soluble forms can be secreted by an appropriate host cell (see page 12, lines 3-10). Browning et al. further teach that such soluble receptors can be prepared as either a soluble extracellular domain, or as chimeric proteins with the extracellular ligand binding domain coupled to an immunoglobulin Fc domain. See page 18, lines 13-18.

The teachings of Gastinel et al., Lauffer et al., Laping et al., Lo et al., and Browning et al. indicate that those of skill in the art recognized certain technical obstacles that may arise when working with transmembrane proteins. In addition, these references indicate that in order avoid such obstacles, it was known to use soluble forms of such transmembrane proteins (for example, proteins lacking the transmembrane region and/or soluble receptor-Fc fusion proteins) in place of the full-length, membrane-bound proteins.

In this regard, it is noted that in addition to identifying BST-2/HM1.24 as a transmembrane protein, Ishikawa et al. (discussed above) also constructed a **soluble** form of BST-2/HM1.24, in which the putative extracellular region of was fused to the Fc region of human IgG1 (see page 527, right column, "Production of soluble recombinant BST-2/HM1.24-immunoglobulin fusion protein"; and also at page 530, left column, first paragraph; and Figure 4).

When taken together with the teachings of Gastinel et al., Lauffer et al., Laping et al., and Lo et al. and Browning et al., it would have been obvious to one of ordinary skill in the art to employ a soluble form of the BST-2/HM1.24 antigen when performing antibody-capture assays for anti-HM1.24 antibodies according to the method of Harlow & Lane and Ishikawa et al. More particularly, it would have been obvious to employ BST-2/HM1.24 antigen in which the transmembrane domain had been removed. One would be motivated to use a soluble form instead of the full-length antigen because to avoid potential technical problems known to arise when using full-length transmembrane receptors. For example, it would have been obvious to remove the transmembrane domain and express the extracellular domain of the BST-2/HM1.24 antigen as a fusion protein with Fc as done by Ishikawa et al., in order to enhance production of

the antigen using this known Fc fusion protein system (as also taught by Lauffer et al., Laping et al., and Lo et al.).

With respect to the limitation that the soluble HM1.24 antigen protein used in the method is one "consisting the amino acid sequence modified by lacking the last 17 amino acid residues from a C-terminus in the amino acid sequence of SEQ ID NO:20", Ichikawa et al. illustrate a soluble BST-2/HM1.24 antigen fused to Fc as discussed above. This fusion protein therefore does not *consist* of the indicated amino acid sequence, since it contains the Fc region in addition to amino acids of BST-2/HM1.24.

However, the prior art as discussed above suggests at least two possible ways at arriving at the claimed invention.

First, in light of the teachings of Gastinel et al. and Browning et al. that soluble forms of a transmembrane receptor may be produced either by deletion of the transmembrane domain or alternatively via construction of an Fc fusion protein, it would have been obvious to one of ordinary skill in the art to prepare the soluble HM1.24 antigen protein by simply removing the transmembrane domain, rather than through use of an Fc fusion as in Ishikawa.

One would be motivated to prepare soluble HM1.24 in this manner because Matsuzawa et al. taught that it was known in the art that Fc sequences may result in nonspecific binding when used in *in vitro* immunoassays. Therefore, one would be motivated to remove the Fc sequence from the soluble HM1.24 antigen protein prior to its use in such an immunoassay in order to avoid these known problems.

Alternatively, in light of the teachings of Laping et al., Lo et al., and Matsuzawa et al. as discussed in detail above, it would have been obvious to one of ordinary skill in the art to first

produce the soluble BST-2/HM1.24 as an Fc fusion protein and then to subsequently cleave off the Fc region. In particular, these references indicate that it was known in the art to exploit Fc fusion proteins to express and purify soluble proteins, and also that it was known to subsequently remove the Fc tag. As such, it would have been obvious to prepare soluble BST-2/HM1.24 as a fusion protein with Fc (as illustrated by Ishikawa et al.) and then to subsequently cleave off the Fc region, via use of a cleavable linker as taught by Laping et al. and Lo et al.

One would be motivated to do this since as recognized by Laping et al., it can be desirable to delete the Fc part after the fusion protein has been expressed and purified. Additional motivation is provided by Matsuzawa et al. who taught that it was known in the art that Fc sequences may result in nonspecific binding when used in *in vitro* immunoassays. Therefore, one would be motivated to remove the Fc sequence from the soluble HM1.24 antigen protein prior to its use in such an immunoassay in order to avoid these known problems.

It is also noted that Ishikawa et al. employed a secretory signal sequence from BST-1 in their Fc fusion construct (page 530, left column). However, such sequences were known to be removed by the host cell (Lo et al. column 5, lines 18-32). Even if this did not occur naturally in the host cell, Lo et al. teach that such sequences are cleaved (column 2, lines 18-37; see also Figure 1). It is also noted that because the secretory signal sequence is appended at the amino terminus prior to the Fc region, it would also be cleaved off upon removal of the Fc region.

The claim limitation of "a protein consisting the amino acid sequence modified by lacking **the last 17 amino acid residues** from a C-terminus in the amino acid sequence of SEQ ID NO:20" is also interpreted to refer to the amino acid sequence SEQ ID NO:20 in which the last 17 residues of this sequence are absent.

The Examiner notes that the soluble BST-2/HM1.24-immunoglobulin fusion protein taught by Ishikawa et al. corresponds to the portion of HM1.24 from asparagine 49 to serine 162 (see page 527, right column, "Production of soluble recombinant BST-2/HM1.24-immunoglobulin fusion protein"; and also at page 530, left column, first paragraph; and Figure 4). Comparing the sequence information in Figure 4 of Ishikawa et al. with instant SEQ ID NO:20, it can be seen that the sequence Asn 49 to Ser 162 corresponds to the amino acid sequence shown in SEQ ID NO:20, but lacking **the last 18 amino acid residues** of SEQ ID NO:20.

As such, the BST-2/HM1.24 fusion protein of Ishikawa also lacks the last 18, rather than the last 17 residues, of SEQ ID NO:20.

However, the examiner notes that the instant claims require only that the antigen lack 17 the last amino acids. Because the antigen protein of Ishikawa et al. lacks the last 18 amino acids, it also necessarily lacks the last 17 amino acids. As a result in which this manner in which the invention is being claimed, the teaching of an antigen protein lacking the last 18 amino acids (as in Ishikawa et al.) reads on the instantly claimed protein.

Even presuming that Applicant intends to claim an antigen protein which lacks exactly 17 (and no more) amino acids, the claimed invention is considered obvious for the following reasons.

As noted above, the BST-2/HM1.24 fusion protein of Ishikawa lacks the last 18, rather than precisely the last 17, residues of SEQ ID NO:20.

<u>Figure 4 of Ishikawa:</u>

```
                                               GTGGAATTC   9

ATG GCA TCT ACT TCG TAT GAC TAT TGC AGA GTG CCC ATG  48
Met Ala Ser Thr Ser Tyr Asp Tyr Cys Arg Val Pro Met  13

GAA GAC GGG GAT AAG CGC TGT AAG CTT CTG CTG GGG ATA  87
Glu Asp Gly Asp Lys Arg Cys Lys Leu Leu Leu Gly Ile  26

GGA ATT CTG GTG CTC CTG ATC ATC GTG ATT CTG GGG GTG 126
Gly Ile Leu Val Leu Leu Ile Ile Val Ile Leu Gly Val  39

CCC TTG ATT ATC TTC ACC ATC AAG GCC AAC AGC GAG GCC 165
Pro Leu Ile Ile Phe Thr Ile Lys Ala Asn Ser Glu Ala  52

TGC CGG GAC GGC CTT CGG GCA GTG ATG GAG TGT CGC AAT 204
Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg Asn  65
                                                *
GTC ACC CAT CTC CTG CAA CAA GAG CTG ACC GAG GCC CAG 243
Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln  78

AAG GGC TTT CAG GAT GTG GAG GCC CAG GCC GCC ACC TGC 282
Lys Gly Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys  91

AAC CAC ACT GTG ATG GCC CTA ATG GCT TCC CTG GAT GCA 321
Asn His Thr Val Met Ala Leu Met Ala Ser Leu Asp Ala 104
 *
GAG AAG GCC CAA GGA CAA AAG AAA GTG GAG GAG CTT GAG 360
Glu Lys Ala Gln Gly Gln Lys Lys Val Glu Glu Leu Glu 117

GGA GAG ATC ACT ACA TTA AAC CAT AAG CTT CAG GAC GCG 399
Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln Asp Ala 130

TCT GCA GAG GTG GAG CGA CTG AGA AGA GAA AAC CAG GTC 438
Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val 143

TTA AGC GTG AGA ATC GCG GAC AAG AAG TAC TAC CCC AGC 477
Leu Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser 156

TCC CAG GAC TCC AGC TCC GCT GCG GCG CCC CAG CTG CTG 516
Ser Gln Asp Ser Ser Ser Ala Ala Ala Pro Gln Leu Leu 169

ATT GTG CTG CTG GGC CTC AGC GCT CTG CTG CAG TGAGATC 556
Ile Val Leu Leu Gly Leu Ser Ala Leu Leu Gln ...     180

CCAGGAAGCTGGCACATCTTGGAAGGTCCGTCCTGCTCGGCTTTTCGCTTG 606

AACATTCCCTTGATCTCATCAGTTCTGAGCGGGTCATGGGGCAACACGGTT 657

AGCGGGGAGAGCACGGGGTAGCCGGAGAAGGGCCTCTGGAGCAGGTCTGGA 708

GGGGCCATGGGGCAGTCCTGGGTGTGGGGACACAGTCGGGTTGACCCAGGG 759

CTGTCTCCCTCCAGAGCCTCCCTCCGGACAATGAGTCCCCCCTCTTGTCTC 810

CCACCCTGAGATTGGGCATGGGGTGCGGTGTGGGGGGCATGTGCTGCCTGT 861

TGTTATGGGTTTTTTTTGCGGGGGGGGTTGCTTTTTTCTGGGGTCTTTGAG 912

CTCCAAAAAATAAACACTTCCTTTGAGGGAGAGCAAAAAAAAAAAAAAAAA 963

AAAAAAAAAAAAAAAAAAGAATTCCACCACA                     996
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FIG. 4. Nucleotide and predicted amino acid sequence of human BST-2 cDNA. The putative transmembrane region is underlined. Two potential sites of N-linked glycosylation are indicated by asterisks. This sequence data have been deposited with DDBJ/EMBL/GenBank under Accession No. D28137.

<u>SEQ ID NO:20 as disclosed instantly:</u>

```
<210> 20
<211> 132
<212> PRT
<213> Homo sapiens

<220>
<223> Amino acid sequence of soluble HM 1.24 antigenic
      protein

<400> 20
Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
  1               5                  10                  15

Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
             20                  25                  30

Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
         35                  40                  45

Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
     50                  55                  60

Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln
 65                  70                  75                  80

Asp Ala Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val Leu
                 85                  90                  95

Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser Ser Gln Asp Ser
            100                 105                 110

Ser Ser Ala Ala Ala Pro Gln Leu Leu Ile Val Leu Leu Gly Leu Ser
        115                 120                 125

Ala Leu Leu Gln
    130
```

Therefore, Ishikawa et al. disclose a soluble HM1.24 antigen protein having the amino acid sequence modified by lacking 18 amino acid residues from the C-terminus of SEQ ID NO:20, while the instantly claimed invention recites a protein modified by lacking 17 amino acid residues from the C-terminus of SEQ ID NO:20. In other words, the instant claims invoke proteins comprising the sequence from amino acids 49 to 163 of full-length HM1.24, while the soluble HM1.24 antigen protein of Ishikawa et al. ranges from amino acids 49 to 162. The Ishikawa et al. protein is missing an additional residue from the C-terminus, namely the alanine residue at position 163 of the full-length protein.

However, the courts have ruled that in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See MPEP 2144.05.

In the instant case, the teachings of Gastinel et al. and Lauffer et al. establish that deleting amino acids from a transmembrane protein was known to have effects on the physical properties of the protein, namely on the protein's solubility. Lauffer et al. further contemplate soluble fusion proteins composed of "various portions of the extracellular domains of human membrane proteins" (column 1, lines 46-56). Such teachings indicate that the particular amino acids sequence of a transmembrane receptor was known to be a result-effective variable.

Therefore, it would have been obvious to one of ordinary skill in the art to vary the amino acid sequence of the soluble HM1.24 antigen protein of Ichikawa et al. by including an additional amino acid at the region corresponding to the C-terminus of HM1.24. In particular, because Ishikawa et al. taught that the next amino acid in the endogenous sequence of HM1.24 is alanine 163, it would have been obvious to include this residue in the construct. Put another way, it would have been obvious to remove 17 rather than 18 amino acids from the C-terminus of HM1.24 when preparing the soluble HM1.24 antigen protein.

Furthermore, when taken together with the general knowledge in the art that the amino acid alanine is a small amino acid that possesses no reactive groups on its side chain, one would have had a reasonable expectation of success including alanine 163 in the soluble HM1.24 antigen protein of Ichikawa et al. because the resulting protein lacking 17 rather than 18 amino acids would be reasonably expected to have the same properties.

In addition, one of ordinary skill in the art would have had a reasonable expectation of success in using the modified soluble HM1.24 antigen protein of Ichikawa et al. to detect anti-HM1.24 antibodies according to the antibody-capture assay format of Harlow & Lane based on the teachings of Gastinel et al. that soluble receptors maintained the ability to bind to antibodies. Similarly, Lauffer et al. taught that soluble fusion protein of transmembrane receptors retain their biological activity.

It is also possible to analyze the teachings of Ichikawa et al. in view of those of Harlow & Lane, Gastinel et al., Lauffer et al., Laping et al., Lo et al., Matsukawa et al., and Browning et al. In particular, although Ichikawa et al. do not specifically direct the skilled artisan to employ the soluble HM1.24 antigen protein for the purpose of detecting anti-HM1.24 antibodies, known uses for antigens included using solid-phased antigen for the purpose of detecting cognate antibodies in immunochemical assays, as taught by Harlow & Lane.

Further, it was known to use soluble forms of transmembrane receptors in place of full-length membrane-bound forms for technical reasons, as taught by Gastinel et al., Lauffer et al., Laping et al., and Lo et al. It was known to produce such soluble forms either by removal of the transmembrane domain (as taught by Gastinel et al. and Browning et al.) or alternatively via Fc fusions was known (as taught by Browning et al., Ishikawa et al., Lauffer et al., Laping et al., and Lo et al.). When choosing the latter course, it was further known to be desirable in some instances to subsequently remove the Fc tag (as taught by Laping et al., Matsukawa et al., and Lo et al.). Finally, although the soluble HM1.24 antigen protein of Ichikawa et al. lacks 18 rather than 17 amino acids from the C-terminus of SEQ ID NO:20, based on the knowledge of the

amino acid sequence of HM1.24 as taught by Ichikawa et al. as well as the general knowledge in the art, one would reasonably expect the two proteins to possess the same properties.

With respect to claim 2, Harlow & Lane teaches binding antigens to a solid phase as discussed above. One would have had a reasonable expectation of success in binding the soluble HM1.24 antigen protein to a solid phase because Gastinel et al. taught that soluble receptors could be attached to any compatible, functional surface (column 10, lines 42-47; column 11, lines 62-67).

With respect to claim 6, Harlow & Lane teaches immobilization of antigens for the antibody-capture assay on microtiter plates (page 563, second paragraph).

With respect to claim 7, Harlow & Lane teaches using a secondary labeled reagent that will specifically recognize the antibody (i.e., a primary antibody against the antibody). See page 563, first paragraph and page 564. Therefore, when conducting antibody capture assays using soluble HM1.24 antigen protein to detect anti-HM1.24 antibodies as discussed above, it would have been further obvious to employ a labeled reagent that specifically recognized anti-HM1.24 antibodies in order to detect antigen-antibody binding.

With respect to claim 13, Harlow & Lane discuss how all immunoassays rely on labeled reagents for detection (pages 591-592). Suitable labels include radioactive compounds, enzymes, biotin, or fluorochromes (page 591, first paragraph).

With respect to claim 18, Harlow & Lane teach that antibodies circulate through the blood and lymph (see page 7). The teachings of Ishikawa et al. relate to *human* HM1.24. Therefore, when detecting HM1.24 antibodies according to the prior art methods as discussed

above, it would have been further obvious to detect the antibodies in human fluids such as blood or lymph, as one of ordinary skill in the art would expect to find antibodies in these fluids.

8. Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Ishikawa et al., Gastinel et al., Lauffer et al., Laping et al., Lo et al., Matsuzawa et al., and Browning et al. as applied to claim 1 above, and further in view of Frank et al. (U.S. 5,646,115).

The references are as discussed in detail above. Harlow & Lane teaches antibody-capture immunochemical assays in which binding of antibody in a test sample to solid phase antigen is detected using an antibody specific to the test antibody. However, the references fail to specifically teach using a second antibody in addition to the antibody specific to the test antibody.

Frank et al. teach immunochemical assays in which antigen (saliva proteins) are immobilized on a solid phase and used to capture antibodies in a body fluid test sample (column 34, line 22 to column 35, line 45). The reference teaches that the amount of antibody bound to the solid phase can be determined using one or more layers of secondary antibodies. For example, an untagged secondary antibody can be bound to a serum antibody (in the test sample) and the untagged secondary antibody can then be bound by a tagged tertiary antibody). See column 35, lines 35-45.

Therefore, it would have been further obvious to one of ordinary skill in the art to employ a second antibody (tagged tertiary antibody) as taught Frank et al. in addition to the primary antibody taught by Harlow & Lane in the method of Harlow & Lane, Ishikawa et al., Gastinel et

al., Lauffer et al., Laping et al., Lo et al., Matsuzawa et al., and Browning et al. in order to achieve the same purpose, namely that of determining the amount of antibody in the test sample that is bound to the solid phase. More particularly, one would be motivated to include an additional antibody layer in this manner in order to determine the amount of anti-HM1.24 antibody in a test sample.

Response to Arguments

9. Applicant's arguments filed 8/13/2010 have been fully considered but are not found persuasive.

10. With respect to the rejections of claims 1-2, 6-7, 13 and 17 under § 103, Applicant argues that one of ordinary skill in the art would not be motivated to subsequently delete the IgG1 Fc domain from the soluble recombinant HM1.24 antigen-Fc fusion protein of Ishikawa. In particular, Applicant argues that the IgG1 Fc used by Ishikawa was obtained by Dr. Seed. Applicant has attached the Seed et al. reference (Zettlmeissl et al., Exhibit A) and argues that this reference teaches that the serum survival is prolonged by fusion to IgG1-Fc. Applicant argues that therefore, one would not be motivated to remove the IgG1-Fc because it would worsen serum survival.

This is not found persuasive because as discussed in detail in the Advisory action mailed 6/29/2010, the evidence of record indicates that it was known in the art to prepare soluble forms of transmembrane receptors simply by removal of the transmembrane domain. As such, a determination of obviousness does not rest on whether one would be motivated to subsequently remove the Fc domain from a soluble HM1.24-Fc fusion protein such as that of Ishikawa et al.

Rather, the record reflects that those of ordinary skill in the art recognized that soluble receptors could be produced simply by removing the transmembrane domain. Although one could also arrive at the claimed invention by preparing a soluble HM1.24-Fc fusion protein and then removing the Fc domain, the issue of patentability cannot be resolved simply by ascertaining whether one would be motivated to carry out this subsequent removal of the Fc domain, since the art recognized other means of preparing soluble receptors.

In summary, there are at least two ways of arriving at the claimed invention suggested by the prior art (i.e., either through simple deletion of the transmembrane domain or through the production and subsequent removal of an Fc domain). See also Browning et al. (WO 96/22788), who discuss these two art-recognized means of preparing soluble receptors at page 18, lines 12-19. Applicant's arguments directed to only one of these scenarios are insufficient to address the rejection.

Notwithstanding the above, the examiner disagrees that one would not be motivated to remove the IgG1-Fc because it would worsen serum survival. Applicant points to the evidence of Exhibit A in support of this argument. Applicant argues that this reference teaches that the serum survival is prolonged by fusion to IgG1-Fc. Applicant argues that it was well known that serum contains various proteases, and therefore when serum and a protein are mixed in an ELISA assay, the protein is hydrolyzed by the proteases in the blood. As best understood, Applicant also takes the position that this proteolysis in an ELISA setting would occur for any "fluids". See Reply, page 6, first paragraph.

Initially, it is noted that Applicant provides no evidence to support these contentions. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d

600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness.").

In particular, Applicant has not provided any evidence to establish that proteolysis of protein reagents being used in ELISA was a significant or documented problem in the art, for which no remedy or solution was known. In addition, Applicant has not provided any evidence to establish that such proteolysis occurs not only for serum for any "fluid" sample as now claimed. It is unclear how the evidence of record supports Applicant's extrapolation from serum to any fluid.

It is true that Zettlmeissl et al. reference teaches that "[b]ecause antibodies are among the longest lived of circulation proteins, CD4:Ig fusion proteins might be expected to show increased serum survival" (see page 350, right column, last paragraph).

However, the reference is referring to the serum half-life of fusion proteins that were injected intravenously into laboratory animals in *in vivo* experiments (ibid). By contrast, the instant claims relate to *in vitro* immunoassay methods in which any fluid test sample is contacted with soluble HM1.24 antigen. While serum half-life might be viewed as critically important when a protein is being injected *in vivo* as a therapeutic, Applicant has not adequately explained or documented why *in vivo* serum half-life would be viewed as critical to the ordinary artisan when carrying out such *in vitro* immunoassay methods, which do not involve injection of the protein into serum *in vivo*. In particular, in immunoassay methods such as those claimed, the test samples are typically only exposed to immobilized antigen for brief periods of time (see, e.g.,

Harlow & Lane at page 564, steps 3-4 in particular). Applicant has not shown that the possibility of proteolysis would have been viewed as a concern when the antigen is only exposed to serum for 2 hours.

In summary, while for other applications (i.e., therapeutic use of a soluble protein) removal of the Fc domain might not be warranted because prolonging serum half-life would be viewed as critical, Applicant has not established why this goal would be critical to an *in vitro* immunoassay method such as that claimed.

Moreover, those of ordinary skill in the art recognized that for in vitro diagnostic applications such as the instantly claimed methods, the presence of Fc sequences may be detrimental.

Matsuzawa et al. (U.S. 5,374,533) recognized that nonspecific interactions can occur between Fc sequences and components in a sample such as rheumatoid factor, which results in nonspecific interactions in immunoassays. See column 2, lines 9-32. To avoid this problem of nonspecific interactions, the authors removed the Fc sequence from their immunoassay reagent (in this case, an antibody). See also column 4, lines 41-55.

Therefore, while Fc sequences may have been recognized to have a functional role *in vivo*, the prior art recognized that such sequences may result in detrimental nonspecific binding in *in vitro* immunoassays. For these reasons, Applicant's arguments that one of ordinary skill in the art would not seek to remove the Fc domain are not found persuasive.

Applicant further argues that according to the present invention, it was newly found that a soluble HM1.24 antigen lacking the C-terminal 17 amino acids <u>can form a dimer without the</u>

need for addition of an Fc sequence for dimer formation. Applicant also argues that the soluble HM1.24 antigen maintains the biological activities of the native protein. See Reply, page 6, third paragraph.

Such arguments have been previously advanced and are not found persuasive for reasons of record as set forth in the advisory action mailed 6/29/2010. In addition, such conclusory statements by counsel do not constitute sufficient evidence of unpredictability or of unexpected results. Applicant has not provided any extrinsic evidence to show that these features would have been unexpected. For example, since Gastinel et al. taught soluble receptors maintain the ability to bind to antibodies, there is insufficient evidence record to conclude that maintenance of biological activity would have been unexpected or unforeseen.

Applicant further argues that one would not be motivated to remove the Fc sequence for use to detect or determine a soluble HM1.24 antigen protein at low concentrations (Reply, page 6, last paragraph to page 7, second paragraph).

This is not found persuasive because as discussed in the advisory action mailed 6/29/2010, it is not apparent how such arguments bear on instant claims, which are directed to an assay for detecting anti-HM1.24 **antibody** and not HM1.24 antigen (or in particular HM1.24 protein at "low concentration").

Applicant does not separately argue the limitations of dependent claims 8-9 (see Reply, page 7).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Christine Foster/
Examiner, Art Unit 1641